

REMARKS

Entry of the foregoing and further and favorable reconsideration of the subject application pursuant to and consistent with 37 C.F.R. §1.112 is respectfully requested.

By the present amendment, the Abstract has been amended as suggested by the Examiner. Claim 26 has been deleted without prejudice to or disclaimer of the subject matter contained therein. Claims 1, 6, 8-10, 13, 15, 16, 18, 21-25, and 27-30 have been amended in order to more precisely define the invention claimed therein. New claim 31, dependent from claim 28, has been added. This new claim derives support from throughout the specification and claims as originally filed. No new matter has been added.

Turning now to the Official Action, the Examiner notes at page 2 that the Abstract of the Disclosure in the present specification "should avoid using phrases which can be implied, such as 'The disclosure concerns,' 'the disclosure defined by this invention,' 'The disclosure describes,' etc." Accordingly, by the present amendment the Abstract in the instant case has been amended to delete the phrase "Disclosed are" and substitute therefor "The present invention provides."

The Examiner also reminds Applicants, at page 2 of the Official Action, that "an English translation of a non-English-language application must be accompanied by a statement that the translation is accurate." Accordingly, such a signed declaration is attached hereto.

Claims 1-30 are rejected under 35 U.S.C. §112, second paragraph, as purportedly indefinite. This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

At page 3 of the Official Action, the Examiner asserts that the term "substance" renders the claims indefinite because the term is given more than one meaning in the claims. Applicants maintain that these claims, like all of the originally filed claims, fully comply with the requirement of 35 U.S.C. §112. Nevertheless,

without conceding to the Examiner's arguments, claims 8, 15, 18, and 27 have been amended to replace the term "substance" with the term "label."

The Examiner further asserts, at page 3 of the Official Action, that claims 1-8 and 9-16 are indefinite because they lack a mutation detection step. Without conceding to the Examiner's arguments, but solely in an effort to expedite prosecution, claims 1 and 9 have been amended to conclude with a mutation detection step

The Examiner asserts, at page 4 of the Official Action, that claims 6-8 "lack proper antecedent basis because Claim 1 does not recite quantification." Without conceding to the Examiner's arguments, but solely in an effort to expedite prosecution, claim 6 has been amended in order to clarify that the quantification does not depend for antecedent basis from claim 1.

The Examiner further asserts, at page 4 of the Official Action, that claims 1, 9, 13, and 15 "are indefinite because 'substrate' is given two different meanings in the claims." Without conceding to the Examiner's arguments, but solely in an effort to expedite prosecution, claims 13 and 15 have been amended to delete the term "substrate."

The Examiner also asserts, at page 4 of the Official Action, that claim 10 is indefinite because "it is not established that fragments are fixed at 5' ends *i.e.* the 3' ends are free." Without conceding to the Examiner's arguments, but solely in an effort to expedite prosecution, claim 10 has been amended to recite that the 5' ends are fixed to the substrate.

The Examiner asserts, at page 4 of the Official Action, that claim 15 lacks proper antecedent basis for the limitation "substrate is labeled." Without conceding to the Examiner's arguments, but solely in an effort to expedite prosecution, claim 15 has been amended as suggested by the Examiner.

The Examiner also asserts, at page 4 of the Official Action, that claims 16-18 "lack proper antecedent basis because Claim 9 does not recite quantification." Without conceding to the Examiner's arguments, but solely in an effort to expedite

prosecution, claim 16 has been amended such that the quantification recited therein does not depend for antecedent basis from claim 9.

In view of these amendments, withdrawal of this rejection is respectfully requested.

Claims 23-25 are rejected under 35 U.S.C. §102(e) as purportedly anticipated by Gifford (U.S. Patent 5,750,335). This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

In order to anticipate a claim under 35 U.S.C. §102, a reference must teach every element of the claim. See MPEP 2131 *et seq.* The Examiner argues, at page 5 of the Official Action, that Gifford discloses the MutS protein claimed in claims 23-25. Applicants do not concede to the Examiner's arguments regarding the purported disclosure of Gifford. Nevertheless, in an effort to expedite prosecution, claims 23-25 have been amended: claim 23 recites that the substance claimed therein is labeled with GFP (Green Fluorescence protein). Claim 25 has been limited to C/C mismatch binding proteins. Claim 24 recites C/C mismatch binding proteins labeled with GFP. Gifford neither discloses, nor suggests, either C/C mismatch binding proteins, nor the use of GFP as a label. As defined at pages 8 and 12 of the present application, MutS is may be efficiently employed to detect G/T or G/A mismatches, but is not optimally employed ("very weak") to detect C/C mismatches. Likewise, C/C proteins are not efficiently employed to bind the same bases as MutS. This means that MutS and C/C proteins are not functional analogs, but in fact have contrasting activities. Therefore, even assuming *arguendo* that Gifford teaches the use of MutS proteins or analogs, such a teaching would not extend to C/C proteins. Consequently, Gifford neither teaches nor suggests all of the limitations of the rejected claims. Withdrawal of this rejection is thus respectfully requested.

Claims 23-26 are rejected under 35 U.S.C. §103 as purportedly obvious over Gifford as set forth above, and further in view of Chee et al. (U.S. Patent 5,837,832). This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

The requirements of a *prima facie* case of obviousness are set forth in MPEP 2143:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The deficiencies of the Gifford patent are discussed in detail above. The Examiner asserts, at page 6 of the Official Action, that one of ordinary skill in the art would have been motivated to combined the disclosure of Gifford, as discussed above, with the disclosure of fluorescent labeling by Chee et al. to arrive at the presently claimed invention. Chee et al. do not remedy the deficiencies of Gifford, as they neither disclose nor suggest the use of C/C mismatch binding protein, as required by the present claims.

With regard to the use of fluorescent label, Applicants note that GFP is a very specific label, not a general-purpose fluorescent label. Chee et al. describe the fluorescent labeling of nucleic acids (col 21, lines 1-18), and not the labeling of other substances (such as proteins) with a fluorescent label. As taught in the present application, substances specifically bindable mismatched base pair are a very specific kind of substances which require a manner of labeling which is different from the manner of labeling nucleic acid as disclosed by Chee et al. In other words, one of ordinary skill in the art would not expect to successfully extrapolate from the disclosure of fluorescently labeled nucleic acids, described by Chee et al., to the GFP-labeling of the present invention.

Applicant note that Gifford refers to labeled MutS protein, while Chee et al. refers to labeled nucleic acid. The Examiner has pointed to no suggestion or motivation, either in the cited patents or in the knowledge generally available to one of ordinary skill in the art, to combine the teachings of the two patents. The only apparent motivation to combine these two disclosures rests within the instant

application. Moreover, Applicants respectfully submit that a careful review of the cited patents reveals that one of ordinary skill in the art would not derive a reasonable expectation of success from these patents with regard to the subject matter of the present claims. Finally, the cited patents, taken together, do not disclose or suggest all of the limitations of the present claims. Accordingly, the present claims are not *prima facie* obvious over Gifford in view of Chee et al. Withdrawal of this rejection is thus respectfully requested.

Claims 1-8 and 19-30 are rejected under 35 U.S.C. §103(a) as purportedly obvious over Gifford, in view of Chirikjian et al. (U.S. Patent 5,763,178), and further in view of Chee et al. This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

The requirements of a *prima facie* case of obviousness are set forth above. The Chee et al. describe a "DNA chip" having 100-100,000 probes immobilized on a solid support, wherein said probes have 9 to 20 nucleotides in length (see claim 1). These number of very short probes are overlapping one another in sequence.

Then, the use of MutS or other equivalent proteins is disclosed at column 7, lines 18-24. In one example, the CFTR gene chip (column 7, lines 58-67) bears an array of 1296 probes covering the full length of exon 10 of the CFTR gene arranged in a 36×36 array of 356 λm elements. This "tiling method" (column 8, lines 17-29) which requires that a high number (~1296) of very short probes (preferably 10-18 bases) overlaps in order to cover the full length of an exon (e.g. Exon 10 of CFTR gene).

Chee et al. teach the use of very short probes (10-18 bases; see the sequence listing from columns 13 to 18), and further that small differences in length are very important. At column 21, lines 56-67, in fact, Chee et al. assert that resolution of the different 12-mer targets was better with the 10-mer probe sets than with the 12-mer probe sets.

Chee et al. describe that the probes can be shorter or longer than 12-18 (column 6, lines 4-7), and claim oligonucleotides of 9 to 20 bases (see claim 1).

Accordingly, on the basis of the data disclosed, and especially in consideration of the above example referred to 10-mer and 12-mer sets, Applicants respectfully maintain that one of ordinary skill would not be directed, by the teachings of Chee et al., to the use of more or longer sequences. In contrast, the method of the present application relates to part or all sequence of a full-length gene. For example, Example 1 (page 15) describes the fixation of TSH β cDNA was on the substrate.

In conclusion, one of ordinary skill in the art, at the time the present application was filed, following the teachings of Chee et al. would have been led to use very short probes, and would have been careful to pay attention to small differences in length (see again the example 10-mer vs. 12-mer). One of ordinary skill in the art would not have found any suggestion to extend the use of the Chee et al. chip to a method using part or all of a full length sequence. On the contrary, one of ordinary skill in the art would have been taught away from using long and specific sequences, such as part or all full length sequences.

The Examiner argues that Gifford teaches nucleic acid fragments may be any nucleotide sequence (i.e. cDNA) which encodes a protein. However, a careful review of the cited passage from Gifford (column 4, lines 24-55) reveals that the nucleic acid which encodes the protein in the method of Gifford is the *test* nucleic acid and not the *reference* nucleic acid (i.e., probe), as in the present invention. Gifford does not teach the use of a part or all of a full length sequence as a probe.

In conclusion, none of the cited patents, either alone or in combination, teach or suggest the method of the presently claimed. Withdrawal of this rejection is thus respectfully requested.

Claims 9-18 are rejected under 35 U.S.C. §103(a) as purportedly obvious over Chirikjian et al., in view of Chee et al., and further in view of Goldrick et al. (U.S. Patent 5,891,629). This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

The deficiencies of Chirikjian et al. and Chee et al. are discussed above. The Examiner concedes that Chirikjian et al. does not disclose S1 nuclease, Mung bean

nuclease, or RNase H, but argues that Goldrick et al. "teaches a method for detecting point mutations in nucleic acids using nuclease, *i.e.*, S1 nuclease, Mung bean nuclease and any or all of the RNases." However, Goldrick et al. does not cure the principal deficiencies of the combination of Chirikjian et al. and Chee et al. These two patents, taken together (or alone) neither disclose nor suggest the use of part or all of a full-length sequence as a probe, as required by the present claims. Accordingly, claims 9-18 are not *prima facie* obvious over Chirikjian et al., neither in view of Chee et al., nor further in view of Goldrick et al. Withdrawal of this rejection is thus respectfully requested.

Claims 28-30 are rejected under 35 U.S.C. §103(a) as purportedly obvious over Chee et al. in view of Chirikjian et al. This rejection, to the extent that it applies to the claims as amended, is respectfully traversed.

The deficiencies of Chirikjian et al. and Chee et al. are discussed above. Neither patent discloses, or suggests, the use of part or all of a full-length sequence as a probe, as required by the present claims. Accordingly, claims 28-30 are not *prima facie* obvious over Chee et al. in view of Chirikjian et al. Withdrawal of this rejection is thus respectfully requested.

From the foregoing, further and favorable reconsideration in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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